Official Title:	A Phase II Trial of Doxil, Carboplatin and Bevacizumab in Triple Negative Previously Untreated Metastatic Breast Cancer
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resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

7.2 Dose Calculation

Doses of Doxil or epirubicin will be calculated using the patient's actual weight in the determination of body surface area. A variance of 5% of the calculated total dose will be allowed.

BSA (m^2) =

$$\sqrt{\frac{height(in) x weight(lbs)}{3131}} \quad \text{or} \quad \sqrt{\frac{height(cm) x weight(kg)}{3600}}$$

Doses of carboplatin will be calculated based on serum creatinine using the modified Calvert formula:

Total dose (mg) = Target AUC (mg/ml x min) x [Creatinine Clearance (ml/min) + 25]

Creatinine clearance can either be measured or estimated using the Cockroft-Gault formula, as follows:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

7.3 Treatment Administration

Carboplatin (AUC 5) and either Doxil 30 mg/m^2 or epirubicin 60 mg/m^2 will be administered on Day 1 of each 28-day cycle. Bevacizumab 10 mg/kg will be administered on Day 1 immediately following chemotherapy and alone on Day 15 of each 28-day cycle.

7.3.1 Carboplatin

Carboplatin at target AUC = 5 mg/mL/min will be administered by IV infusion over 30 – 60 minutes.

7.3.2 Doxil

To minimize the risk of infusion-related reactions, the first infusion of Doxil should be administered over 90 minutes, as follows:

- 10 mL over first 10 minutes
- 20 mL over next 10 minutes
- 167 mL/min until completion of the infusion.

If no infusion-related reactions are noted with the initial infusion, subsequent infusions will occur at a rate of 1 mg/minute.

7.3.3 Bevacizumab

Bevacizumab 10 mg/kg will be administered by IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90 ±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 ±10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ±10 minutes.

If a patient experiences an infusion-associated adverse event, she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 ±10 minutes, to a minimum infusion time of 30 minutes, as long as the patient continues to be premedicated. If a premedicated patient experiences an infusion-associated adverse event with the 60 minute infusion, all subsequent doses should be given over 90 ±15 minutes. Similarly, if a premedicated patient experiences an infusion-associated adverse event with the 30 minute infusion, all subsequent doses should be given over 60 ±10 minutes.

7.3.4 Epirubicin

In the event of a shortage of doxil, patients will be allowed to receive epirubicin. Epirubicin will be given by IV administratin over 15 to 20 minutes.

7.4 Dose Modifications

Chemotherapy dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities/adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events, Version 3.0. Patients are allowed a maximum of 2 dose reductions.

If toxicity or adverse events cause one study drug to be held, all study drug doses will be held until criteria is met to resume dosing.

If doxil or epirubicin if used in place of doxil or carboplatin is discontinued the patient will be taken off study. If bevacizumab is discontinued the patient may continue to receive doxil or epirubicin and carboplatin.

Chemotherapy will be held for a maximum of 3 weeks for toxicity or adverse events. If after 3 weeks no recovery is seen, study drugs will be permanently discontinued and the patient will be removed from the study.

Treatment with DOXIL or epirubicin should be discontinued if there is cardiac dysfunction as indicated by:

- symptomatic arrhythmia or congestive heart failure, **or**
- a decrease in LVEF to below the institutional lower limit of normal **and** at least an absolute 5 percentage points decrease from the patient's baseline LVEF value (e.g., 45% to 40%), **or**
- any absolute decrease of 15 percentage points or more from the patient's baseline value (e.g. 60% to 45%).

Dose reduction is planned in case of severe hematological and/or non-hematological toxicities as follows:

Carboplatin: from AUC 5 mg/mL/min to AUC of 4 mg/mL/min

Doxil: from 30 mg/m^2 to 24 mg/m^2

Epirubicin if used in place of doxil will be reduced by 20% from 60 mg/m^2 to 48 mg/m^2.

No additional dose reductions may be given. If toxicity occurs that would indicate a further dose reduction is needed, the patient will be removed from the study. Doses, which have been reduced for toxicity, must not be re-escalated with the exception of liver function tests that improve within ranges given.

HEMATOLOGICAL TOXICITY	
ANC cells/mm^3	**MODIFICATION**
≥ 1,000	Resume treatment with no dose reduction.
< 1000	For ANC < 1,000/mm^3 delay administration until ANC > 1,000. For the first episode, resume treatment at full dose with peg-filgrastim support initiated on Day 2. All remaining cycles may be given with peg-filgrastim at Investigator's discretion. For a second episode, if ANC takes ≤ 3 weeks to recover to > 1,000 with peg-filgrastim support, reduce carboplatin to AUC of 4 mg/mL/min and doxil to 24 mg/m^2 or epirubicin to 48 mg/m^2. If after a 3-week delay ANC has not recovered the patient will be taken off study.
PLATELETS cells/mm^3	**MODIFICATION**
≥ 75,000 -	Resume treatment with no dose reduction.
<75,000	If PLT count was > 25,000/mm^3 and recovers to 75,000/mm^3 within 3 weeks, resume carboplatin and doxil or epirubicin administration at full dose. If platelet count was ≤ 25,000/mm^3 and recovers to 75,000/mm^3 within 3 weeks, reduce carboplatin to AUC of 4 mg/mL/min and maintain the doxil or epirubicin dose. Chemotherapy will be held for a maximum of 3 weeks. If after 3 weeks, no recovery above 75,000/mm^3 is seen the study drugs will be permanently discontinued and the patient will be taken off study.

7.4.1 Carboplatin

Febrile Neutropenia

Febrile neutropenia shall be defined as oral or tympanic fever of ≥ 38.5 °□C or 101.3 °□F in the presence of neutropenia (where neutropenia is defined as ANC < 1000/mm^3). A therapeutic intervention should proceed immediately following the diagnosis of febrile neutropenia. Therapeutic interventions can be as per the institution's guidelines, or may include:

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery of ANC ≥ 1,000/mm^3 or oral temperature < 38.5 °C. This must be documented in the specific adverse event section of the CRFs.

For the first episode, resume treatment at full dose with peg-filgrastim support. If despite peg-filgrastim support, a second episode occurs dose reduce carboplatin to 4 AUC and doxil to 24 mg.m^2. If a third episode occurs the patient will be taken off-study.

Infection With (or Without) Neutropenia

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy, with or without neutropenia, prophylactic G-CSF and prophylactic antibiotics will be added to all remaining cycles. Levofloxacin is recommended at 500 mg oral dose daily for 10 days starting on Day 5 of each cycle for remaining chemotherapy cycles. If levofloxacin is not available or not tolerated, another oral antibiotic must be used. The choice of antibiotic is at the discretion of the Investigator. G-CSF will be added to all subsequent chemotherapy cycles as per ASCO guidelines.

2nd Febrile Neutropenia and 2nd Infection Event

In the case of a second febrile neutropenia or infection event, patient will continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses will be reduced for all remaining cycles. In the case of a 3rd event, there will be no further dose reduction. The patient will stop carboplatin and be removed from the study.

Anemia

In case of Grade 2 decrease in hemoglobin, treatment with blood transfusion or erythropoietin should be given. The use of prohylactic erythropoietin for Grade < 2 anemia is discouraged. The choice of the type of erythropoietin used (long acting or regular) is at the Investigator's discretion. In case of □Grade 3 or 4 decrease in hemoglobin, doses should be reduced as follows: carboplatin reduced from an AUC of 5 mg/mL/min to an AUC of 4 mg/mL/min. Maintain the doxil or epirubicin dose.

Nausea and Vomiting
Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the Investigator. Acute episodes of nausea and vomiting should be controlled with adequate antiemetics. In case of Grade 4 vomiting that persists despite antiemetics, patient will discontinue carboplatin and be removed from the study.

Stomatitis
In case of Grade 4 stomatitis (and/or esophagitis) the patient will discontinue carboplatin and be removed from the study.

Peripheral Neuropathy
If the patient experiences peripheral neuropathy of Grade 2 the following dose modifications should be performed: Delay carboplatin treatment by a maximum of two weeks. As soon as patient recovers, treatment should continue with the following dose recommendations:

- If patient recovers to Grade 1 toxicity, maintain the carboplatin and doxil or epirubicin doses.
- If Grade 2 persists for > 2 weeks, patient will discontinue carboplatin and be removed from the study.

In case of a second episode, maintain the carboplatin dose. If the patient experiences another episode, no further dose reduction is planned and the patient will discontinue carboplatin and be removed from the study.

Cutaneous Reactions
- For Grade 4: Patient will be taken off-study.

7.4.2 Doxil
Patients should be carefully monitored for toxicity. Adverse events, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustment. Following the first appearance of a Grade 2 or higher adverse event, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

HAND FOOT SYNDROME (HFS)	
Toxicity Grade	**Dose Adjustment**
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease doxil dose by 20%.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, patient will be removed from the study. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue doxil treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 20% dose reduction of doxil.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease doxil dose by 20% . If after 2 weeks there is no resolution, Doxil® should be discontinued.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 20% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.

STOMATITIS	
Toxicity Grade	**Dose Adjustment**
1 (painless ulcers, erythema, or mild soreness)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease Doxil®dose by 20%. Maintain the Carboplatin dose.
2 (painful erythema, edema, or ulcers, but can eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, patient will be removed from the study. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose. If patient experience previous Grade 3-4 toxicity, continue treatment with a 20% Doxil® dose reduction.. Maintain the Carboplatin dose.
3 (painful erythema, edema, or ulcers, and cannot eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease Doxil® dose by 20%. Maintain the Carboplatin dose. If after 2 weeks there is no resolution, patient will be removed from the study.
4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose Doxil® by 20%. Maintain the Carboplatin dose.If after 2 weeks there is no resolution, patient will be removed from the study.

7.4.3 Bevacizumab

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued however, patients may continue with doxil or epirubicin and Carboplatin treatment if administration criteria are met.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 7.4.3.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.

7.4.3.1 Infusion Reaction

Infusion of bevacizumab should be interrupted for patients who develop dyspnea or clinically significant hypotension. Patients who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for patients who experience any infusion-associated symptoms not specified above. When the patient's symptoms have completely resolved, the infusion may be continued at no more than 50% of the currently being received rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle (see Section 7.3.3).

Table 7.4.3: Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
No dose modifications for Grade 1 or Grade 2 events	
Grade 3	Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at the Investigator's discretion. Bevacizumab should be held for uncontrolled or symptomatic hypertension present on the day that the bevacizumab dose is to be given. If BP is not controlled to 150/100 mmHg with medication within 1 month, discontinue bevacizumab.
Grade 4 (including RPLS (confirmed by MRI) or hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for Grade 1 or Grade 2 nonpulmonary and non-CNS events	
Grade ≥ 2 pulmonary or CNS hemorrhage	Discontinue bevacizumab.
Grade 3 nonpulmonary and non-CNS hemorrhage	Patients who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other patients will have study treatment held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4	Discontinue bevacizumab.

Table 7.4.3 Bevacizumab Dose Management due to Adverse Events (continued)	
Venous Thrombosis	
[Note: Patients with lung cancer placed on anticoagulant therapy for a thrombotic event should be discontinued from receiving bevacizumab]	
No dose modifications for Grade 1/2 events	
Grade 3/ Asymptomatic Grade 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting study drug treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan.
Symptomatic Grade 4	Discontinue bevacizumab.
Arterial Thromboembolic event	
(Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
No dose modifications for Grade 1 or Grade 2 events	
Grade 3	Hold bevacizumab until resolution to Grade ≤ 1.
Grade 4	Discontinue bevacizumab.
Proteinuria	
No dose modifications for Grade 1 or Grade 2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr, or dipstick 4+)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.

Table 7.4.3 Bevacizumab Dose Management due to Adverse Events (continued)	
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence requiring medical or surgical therapy	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

7.4.4 Epirubicin

In the event that there is a shortage of doxil, patients will be allowed to receive treatment with epirubicin.

Diarrhea and Stomatitis

Antidiarrheal medication may be used at the discretion of the Investigator. Diarrhea ans stomatitis must return to ≤ Grade 1 before administration of the next cycle. If, after a 2 week delay, diarrhea and/or stomatitis have not resolved, therapy must be discontinued.

Grade 1 and Grade 2: No dose reductions.

Grade 3: After the first episode of Grade 3 diarrhea and/or stomatitis, decrease the epirubicine dose to 48 mg/m^2. Maintain the carboplatin dose.

Grade 4: If the patient experiences Grade 4 diarrhea and/or stomatitis, therapy must be discontinued.

Hepatic Dysfunction

Therapy must be held for a ≥ Grade 2 increase in bilirubin (>1.5 x ULN) or Grade 2 increase in SGOT (> 2.5 x ULN). If the increase is not due to metastatic disease, therapy may be resumed at full dose if the following criteria are met:

- SGOT must return to < grade 2 (≤ 2.5 x ULN) within 2 weeks; and
- Bilirubin must return to normal range for the lab within 2 weeks.

7.5 Concomitant Medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. All concomitant medications must be documented in the patient's medical records.

Low-dose aspirin (≤ 325 mg/d) may be continued in patients at higher risk for arterial thromboembolic disease. Patients developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 7.4.3, Bevacizumab Dose Management Due To Adverse Events.

7.6 Supportive Care Guidelines

All supportive measures consistent with optimal patient safety will be utilized, including but not limited to antiemetic medication, hydration, transfusion support and antibiotics. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are participating in this study.

Patients may be started on erythropoietin (Procrit®/Aranesp®) after the first cycle if clinically necessary.

The use of G-CSF for prevention of neutropenia is not allowed. Use of G-CSF or equivalent is to be used in accordance with ASCO Guidelines.

7.7 Adherence/Compliance

Patients who fail to present for treatment appointments may be removed from the study. Patients that are routinely non-compliant to protocol requirements may be removed at the discretion of the Investigator.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician or their designee will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Toxicities (including laboratory abnormalities) will be reported as outlined in the data capture plan.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1 Adverse Event Reporting Requirements

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

All "unexpected" (see Section 8.4) and/or "serious" (See Section 8.2) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the OHRS at (732) 235-7577. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

In addition to reporting to the local IRB, reporting to external bodies such as industry and/or the FDA may be required.

CINJOG affiliates will report all SAEs to the OHRS. OHRS will be responsible for forwarding SAE reports to all appropriate groups as needed

Reporting SAEs using commercially available drugs:
In addition, any unexpected (*not listed in the package insert*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of Doxil and Bevacizumab must be reported to the FDA within 7 working days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

Expedited reporting requirement for adverse events experienced by patients treated with commercial agents only					
Attribution	Grade 4		Grade 5[a]		**Protocol Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely					See footnote (b) for special requirements.
Possible, Probable, Definite	REPORT		REPORT		
FDA MedWatch form 3500: Indicates that an expedited report is to be submitted to the FDA within 7 working days					

a: This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.
b **Protocol-specific expedited reporting requirements:** All SAEs must be reported to Genentech, Inc. as outlined below.

All CINJOG affiliates continue to report all SAEs to the OHRS.

8.1.1 Reporting of Serious Adverse Events to Genentech, Inc.
Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the definitions of a serious adverse event (see Section 8.2).

All STEAEs should be recorded on a MedWatch 3500a Form and faxed to:

G[redacted]
[redacted]

(Please use the safety reporting fax cover sheet provided in the study operations manual for your fax transmission)

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive